

## **1. STUDY DETAILS**

### **1.1 STUDY TITLE**

**Pilot Clinical Evaluation of a Microwave Imaging System for Early Breast Cancer Detection**

### **1.2 REFERENCE NUMBERS**

Protocol identification number: TN.32.1.17.SATF

**NCT number: NCT03475992**

### **1.3 CONTACT DETAILS**

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### 3. SYNOPSIS

Title of study	Pilot Clinical Evaluation of a Microwave Imaging System for Breast Cancer Detection
Name of sponsor/company	MVG Industries SAS
Phase of development	First-in-Human Pilot clinical testing
Objectives	To collect exploratory datasets to guide prototype refinement of a microwave imaging system.
Trial design	Early-phase pilot clinical study on a restricted number of patients.
Key inclusion criteria	<p>Subjects must be able and willing to give written informed consent and to comply with the requirements of this study protocol.</p> <p>Have attended the Symptomatic Breast Unit with a palpable breast lump.</p> <p>Subjects must have had a mammogram in the clinical assessment period (<math>\leq 6</math> weeks before the microwave breast investigation).</p> <p>Subjects must be able to comfortably lie reasonably still in a prone position for up to 15 minutes.</p> <p>Subjects with bra size larger than 32B and cup size larger or equal to B.</p> <p>Subjects whose breast size is adapted to the cylindrical container of the MBI system</p>
Key exclusion criteria	<p>Subjects who are unable to provide written informed consent.</p> <p>Subjects who are pregnant or breast-feeding.</p> <p>Subjects who have had previous surgery on the breast.</p> <p>Subjects who have received chemotherapy or radiotherapy to the breast.</p> <p>Subjects who have had biopsy less than 2 weeks prior to imaging.</p> <p>Subjects with any active or metallic implant (e.g. cardiac pacemaker, stents, internal cardiac defibrillator, cardiac resynchronisation device, nerve stimulator, etc.), or subjects bearing any non-removable metallic object (e.g. piercing) on their torso.</p> <p>Post-biopsy patients whose breast tissue is not healed sufficiently for the imaging procedure, in the opinion of the investigator.</p>

	<p>Patients who have had or plan to have a breast cyst aspiration before MBI.</p> <p>Subjects with significant co-morbidities which, in the opinion of the investigator, may influence the result of the study.</p> <p>Subjects with prior or concurrent malignancy.</p> <p>Subjects under the age of 18 years old.</p> <p>Subjects with evidence of inflammation and/or erythema of the breast as well as any subjects who have a break in the skin which would be in contact with the coupling fluid.</p> <p>Subjects who would be unsuitable for an MBI scan, unlikely to attend a follow up visit, or would otherwise be unsuitable for such an investigation, in the opinion of the Investigator.</p>
Number of subjects scanned	25

#### 4. ABBREVIATIONS

CI	Chief Investigator
CRF	Case Report Form
CRFG	Clinical Research Facility Galway
CSR	Clinical Study Report
DPs	Dielectric Properties
DSMB	Data Safety and Monitoring Board
EM	Electromagnetic
EC	European Commission
EU	European Union
FiH	First in Human
GCP	Good Clinical Practice
HPRA	Health Products Regulatory Authority
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
IMDRF	International Medical Device Regulators Forum
MBI	Microwave Breast Imaging
MVG	MVG Industries SAS
OBCD	Optical Breast Contour Detection
PI	Principal Investigator
PIL	Patient/subject Information Leaflet
REC	Research Ethics Committee
R&D	Research and Development
ROI	Region Of Interest
SAE	Serious Adverse Events
SDV	Source Data Verification
SOPs	Standard Operating Procedures
QC	Quality Control
AE	Adverse Event
ADE	Adverse Device Effect
SADE	Serious Adverse Device Effect
USADE	Unanticipated Suspected Adverse Device Effect

## 5. INTRODUCTION

### 5.1 BACKGROUND INFORMATION

Breast cancer is one of the most important cancers to affect women worldwide. Approximately 425,000 new cases of breast cancer are diagnosed every year in Europe resulting in 129,000 deaths[1]. Earlier detection and intervention is considered to be the most important factor in improving the survival rates. X-ray mammography remains the standard imaging modality used for the early-stage detection of the breast cancer. Despite the fact that X-ray mammography provides high resolution images, its limitations in terms of specificity and sensitivity are well known. In the US, one in five cancers is missed by conventional mammography, three in four identified malignancies are later found to be benign [2] and one-fourth cancers are over-diagnosed (never progressing or regressing cancer)[3,4]. Sensitivity is even lower in younger women due to higher dense-to-fatty tissue ratio[4,5]. In addition, mammography requires an uncomfortable and often painful breast compression [6] and its ionizing radiation may not be safe[7].

Microwave imaging is an emerging imaging modality for the early detection of breast cancer. The physical basis of microwave imaging is the dielectric contrast between healthy and cancerous breast tissues at microwave frequencies. Microwave imaging can potentially be used for monitoring neoadjuvant chemotherapy treatment[8], breast health monitoring[9], and for routine screening and diagnosis of breast cancer at the early-stage[10]. The non-invasive and the non-ionizing characteristics of microwaves should allow for frequent scans of the breast using microwave imaging, unlike X-ray mammography[11]. In addition to safety, microwave imaging does not require uncomfortable breast compression and it is potentially a low-cost modality. Several research groups have developed and optimised hardware prototypes for microwave imaging. However, most prototypes are still at pre-clinical stage and very few have been used in clinical studies, demonstrating promising results [8,9,11,12]

The R&D department of MVG is currently developing a prototype of a Microwave Breast Imaging (MBI) system for early breast cancer detection. The system, at its actual stage of development, has been only experimentally tested, using phantoms that simulate the real breast.

The breast phantom repository published by the University of Wisconsin [13] has been used to define MRI-based realistic breast geometries. Using this input, breast moulds have been 3D printed. The moulds have been further filled with appropriate liquid materials, considering the state-of-art knowledge in terms of dielectric properties (DPs) of the breast tissues in the frequency range of interest [14–16]. Appropriate solid materials have accordingly been used to simulate both the skin layer surrounding the breast and the tumour inclusions.

Promising results, in terms of detectability of a tumour of few (6-10) millimetres hidden in the fibro-glandular tissue, have been obtained. Clinical evaluation through human studies has not been performed yet. The current aim is to bring this system prototype to an early-phase pilot clinical study.

### 5.2 RATIONALE FOR THE STUDY

The investigational medical imaging device to be trialed is called “low-power microwave breast imaging system”. It is a low-power electromagnetic (EM) wave breast imaging device for cancer screening purposes.

The investigational medical imaging device consists of two subsystems, both performing a non-invasive examination:

- the Microwave Breast Imaging subsystem (MBI subsystem);
- the Optical Breast Contour Detection subsystem (OBCD subsystem);

The MBI subsystem is an active device which uses non-ionizing radiation. It illuminates the breast with low-power EM waves in the microwave frequency spectrum, which penetrate the breast under examination. The subsystem collects the scattered EM waves and recovers useful information on the breast tissue consistency, given the dielectric contrast of these tissues.

Multi-static radar detection technology is employed in the MBI subsystem for breast image formation.

The well-established MVG technology for fast antenna measurement[17], using multiple sensors in a vertical arch configuration, has been transposed to a horizontal arch of sensors. In addition, vertical translation of the horizontal arch has been enabled, such that 3D multi-static short-range radar imaging is possible.

The sensors are in contact with a cylindrical container filled with a liquid; the so-called coupling liquid has been designed to have EM properties appropriately selected such that the EM wave penetration in the breast is maximized.

During the MBI scan, the patient will be lying, in a face down position on a special bed, integrated with the MBI subsystem. The breast under examination will be immersed in the coupling liquid, through a dedicated circular opening of the bed. The breast will then be scanned. This vertical scan will take approximately 10-15 minutes to complete, depending on the size of each breast.

In order to compute the required volume of coupling liquid, such that the container of the MBI subsystem is optimally filled after immersion of the breast, a simple process for optical assessment of the total volume of the breast will take place just before starting the MBI scan.

The OBCD subsystem serves to provide the total volume of the breast, and also its external contour, as a priori information to the MBI subsystem. The OBCD subsystem consists of a 3D optical camera placed below the examination table, at a distance of several tens of centimetres below the breast. An azimuthal scan of the 3D camera permits to reconstruct the external surface of the breast.

In order for the breast contour to be useful a priori information for the MBI subsystem, it is important that the patient is lying in the same face down position during both the MBI and OBCD scans. Thus, an identical examination table, as the one integrated with the MBI subsystem, is also integrated with the OBCD subsystem.

During the OBCD scan, the patient will be lying on the examination table, with her breast under examination inserted in the circular opening of the examination table. For this scan, there is no coupling liquid; the breast will be in the air, hanging below the examination table.

The clinical data that will be collected in the context of this study is intended to provide early safety information for the proposed investigational medical imaging device. In addition, this exploratory data will guide the refinement of the device hardware and the imaging algorithm design, before a decision is made to proceed (or not) with further clinical tests.

Furthermore, this study will be used to guide sample size calculation for a subsequent study designed to evaluate efficacy, should that appear warranted once this study is completed.

## **6. STUDY OBJECTIVES AND ENDPOINTS**

### **6.1 PRIMARY OBJECTIVE**

To gather exploratory data to refine the investigational medical imaging device.

To establish the safety profile of the investigational medical imaging device.

### **6.2 EXPLORATORY OBJECTIVE**

To investigate the capacity of microwave imaging to detect and characterise pre-existing breast cancer.

### **6.3 SAFETY END-POINT**

To demonstrate that the investigational medical imaging device is safe; This will be measured by the number of Serious Adverse Events and Serious Adverse Device Effects during the total duration of the trial.

## 7. TRIAL DESIGN

### 7.1 GENERAL CONSIDERATIONS

This is a single-site early-phase pilot clinical study. It will take place at Galway University Hospital/ HRB Clinical Research Facility, Galway.

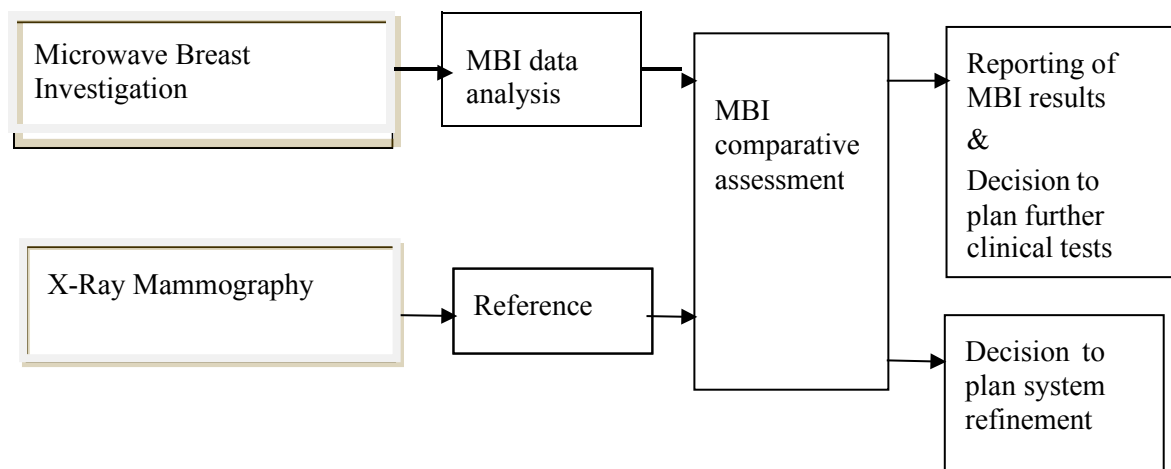
Patients will have a conventional history and breast examinations (Mammogram and / or Ultrasound and Clinical assessment) performed by the physician, as per normal practice in the Symptomatic Breast Unit of University Hospital Galway.

If patients are interested in the study, provide written informed consent and are deemed eligible, they will attend the Clinical Research Facility Galway for an MBI scan. The data from the scan will be collected and stored securely. Patients will be followed up 7-21 days after the microwave breast investigation or before surgery, whichever comes first. Patients will be assessed for their experience of the microwave breast investigation, and for any adverse events.

The written radiology reports from conventional imaging will be acquired and used to evaluate the performance of the MBI subsystem in terms of detecting and estimating size and consistency of the breast lump.

MBI data analysis will be performed off-line, at MVG premises (France), and is expected to be completed few months after the end-date of data collection. Following the assessment of the MBI results by the medical experts involved in the study, a decision will be made regarding the potential of this emerging imaging modality and the interest in proceeding with clinical studies involving larger sample sizes. Based on these results, MVG will decide and plan actions for refinement of the system, towards an upgraded version to be used for potential future tests with a more significant impact.

*Figure 1: Study Schema*



### 7.2 SELECTION OF STUDY POPULATION

This is an early-phase pilot clinical study, thus a cut-off of no more than 30 patients will be scanned.

The study will be orientated to women presenting to the symptomatic breast unit with a palpable breast lump.

The study will be performed on 3 groups of patients:

- **Group 1: Approximately 15 patients** with pre-diagnosed breast cancer (core needle biopsy performed  $\geq 14$  days before the microwave breast investigation).
- **Group 2: Approximately 10 patients** with breast cyst. No prior biopsy.
- **Group 3: Approximately 5 patients** with pre-diagnosed benign lesion (core needle biopsy performed  $\geq 14$  days before the microwave breast investigation).

### 7.3 STUDY PROCEDURES AND ASSESSMENTS

The schedule of events and study-related procedures is summarized in Figures 2, 3 & 4 below.

*Figure 2: Schedule of events for patients in Group 1 - Pre-diagnosed breast cancer (prior core needle biopsy).*

Procedures	<sup>†</sup> Visit 1	<sup>‡</sup> Visit 2	<sup>§</sup> Visit 3
Written informed consent	<b>x</b>		
Confirmation of Inclusion/Exclusion Criteria	<b>x</b>	<b>x</b>	
Compiling Results from Standard of Care Triple Assessments	<b>x</b>	<b>x</b>	
Adverse Event Review		<b>x</b>	<b>x</b>
Demographics	<b>x</b>		
Medical History	<b>x</b>		
Targeted Physical examination	<b>x</b>	<b>x</b>	
Pregnancy Test (prior to MBI procedure)		<b>x</b>	
Patient Clinical Breast / Skin Assessment			<b>x</b>
Microwave Breast Investigation (OBCD scan and MBI scan)		<b>x</b>	
Patient Experience Questionnaire		<b>x</b> *	

Adverse Event Review will only occur once the patient is consented and deemed eligible for the study.

<sup>†</sup> On the day the patient received their biopsy results

<sup>‡</sup>  $\geq 14$  days post biopsy and  $\leq 6$  weeks post mammogram

<sup>§</sup> 7-21 days post MBI, or before surgery, whichever occurs first. (If the patient is unable to attend, the visit can be carried out by telephone)

\* If not done at Visit 2, must be done before study end.

Figure 3: Schedule of events for patients in **Group 2** - Breast cyst - (no prior biopsy)

<b>Procedures</b>	<b>†Visit 1</b>	<b>‡Visit 2</b>	<b>§Visit 3</b>
Written informed consent	<b>x</b>		
Confirmation of Inclusion/Exclusion Criteria	<b>x</b>	<b>x</b>	
Compiling Results from Standard of Care Triple Assessments	<b>x</b>		
Adverse Event Review		<b>x</b>	<b>x</b>
Demographics	<b>x</b>		
Medical history	<b>x</b>		
Targeted Physical examination	<b>x</b>	<b>x</b>	
Pregnancy test (prior to MBI procedure)		<b>x</b>	
Patient Clinical Breast / Skin Assessment			<b>x</b>
Microwave Breast Investigation (OBCD scan and MBI scan)		<b>x</b>	
Patient Experience Questionnaire		<b>x*</b>	

Adverse Event Review will only occur once the patient is consented and deemed eligible for the study.

† On the day of presentation to symptomatic breast unit

‡ ≥ 3 days after Visit 1 to ≤6 weeks post mammogram

§ 7-21 days post MBI (If the patient is unable to attend, the visit can be carried out by telephone)

\* If not done at Visit 2, must be done before study end.

Figure 4: Schedule of events for patients in **Group 3** - Pre-diagnosed benign lesion (prior core needle biopsy).

<b>Procedures</b>	<b>†Visit 1</b>	<b>‡Visit 2</b>	<b>§Visit 3</b>
Written informed consent	<b>x</b>		
Confirmation of Inclusion/Exclusion Criteria	<b>x</b>	<b>x</b>	
Compiling Results from Standard of Care Triple Assessments	<b>x</b>	<b>x</b>	
Adverse Event Review		<b>x</b>	<b>x</b>
Demographics	<b>x</b>		
Medical history	<b>x</b>		
Targeted Physical examination	<b>x</b>	<b>x</b>	
Pregnancy test (prior to MBI procedure)		<b>x</b>	
Patient Clinical Breast / Skin Assessment			<b>x</b>

Microwave Breast Investigation (OBCD scan and MBI scan)		<b>x</b>	
Patient Experience Questionnaire		<b>x*</b>	

Adverse Event Review will only occur once the patient is consented and deemed eligible for the study.

† On the day of presentation to symptomatic breast unit or the day the patient received their biopsy results

‡  $\geq 14$  days post biopsy and  $\leq 6$  weeks post mammogram

§ 7-21 days post MBI or before surgery whichever occurs first. (If the patient is unable to attend, the visit can be carried out by telephone).

\* If not done at visit 2, must be done before study end.

The MBI scan will take place at the CRFG and will be performed by a trained research engineer, assisted by a trained researcher of the study team.

A physician will be always present during the microwave breast investigation, to monitor the health of the participants.

Both the breast bearing the palpable lump and the contralateral breast will be scanned.

The contralateral breast scan will serve as control in the data analysis. The total breast volume will be measured before starting the MBI scan. This *a priori* information on the breast volume will be used to compute the required volume of coupling liquid, such that the container of the MBI subsystem is optimally filled, after immersion of either breast.

The recorded data will be checked and in the case of non-optimal positioning of the patient, the scan may be repeated.

End of Study Visit:

The patient will be seen at the clinic where possible or else phoned 7-21 days after the microwave breast investigation (or before surgery where applicable, whichever comes first) in order to be assessed for adverse events, and the patient clinical breast/skin assessment.

Data stored:

Data from the reference breast imaging modality (X-Ray Mammography) will be collected. An Ultrasound or MRI scan of the patient, if available, will be also provided as reference (in addition to the mammogram). Results of the triple assessment standard of care, including the biopsy results, will be captured as well for reference information. Subgroup analyses to compare the MBI results to Ultrasound and MRI in any patients who underwent such scans as part of routine care will be performed accordingly.

Encrypted data will be generated from the MBI subsystem and the OBCD subsystem. All radiology images and test data will be anonymised by removing any personal or identifiable details and assigning the patient a number. The anonymised data will be transferred to a secure database designed and maintained by the CRFG, then shared with the sponsor.

## 7.4 DATA ANALYSIS

Interim Data Analysis/Reviews:

An interim data analysis will be scheduled after the 10 first patients have been scanned.

A Data Safety and Monitoring Board (DSMB) will be convened. The DSMB will consist of 3 members with appropriate experience in the area and being independent of the study team and the sponsor. The DSMB will review adverse events and data acquisition, in order to decide if continuation of the study is safe and reasonable.

Further data reviews will be performed with the clinical and radiology site team after each 10 patients have been scanned. A target of no more than thirty (30) patients are intended to be scanned. The study data collected is intended to inform sample size calculation for any subsequent study to evaluate efficacy.

The final data analysis on the full cohort of patients enrolled in the study will be performed after the end-of-study, defined as the date of the database lock. The final data analysis will be performed using the MBI images and associated Regions-Of-Interest (ROI) detections and associated features, as extracted after MBI image post-processing. Structural characterization of the lesions as well as sizing of the lesions, will be included in this analysis.

After completion of the data analysis by the sponsor, the MBI results will be provided to two (2) independent consultant radiologists who specialize in breast radiological examinations.

Each radiologist will compare the reference clinical images (mammograms and ultrasound images when available) to MBI imaging findings and conclusions from each will be recorded in relation to the clinical relevance and diagnostic added value of the MBI findings. The two (2) assessments will be performed independently from each other, such that a first estimate of the inter-rater reliability can be extracted.

The Data Analysis will be performed using four (4) analysis sets, as specified below:

- Analysis Set #1: includes the patients with a pre-diagnosed Invasive Ductal Carcinoma (MBI data for the breast with pathology)
- Analysis Set #2: includes the patients with a pre-diagnosed Invasive Lobular Carcinoma (MBI data for the breast with pathology) – if sufficient data is available.
- Analysis Set #3: includes the patients with a biopsy-confirmed solid benign lesion (MBI data for the breast with pathology)
- Analysis Set #4: includes the patients with simple cysts (MBI data for the breast with pathology)

*Table 1: The list of analyses and analysis sets*

<b>Analyses</b>	<b>Analysis Set #1</b>	<b>Analysis Set #2</b>	<b>Analysis Set #3</b>	<b>Analysis Set #4</b>
Pre-diagnosed Palpable Breast Lesion Detectability	✓	✓	✓	✓
Breast Lesion Sizing: comparison against post-surgery histology data and conventional imaging data (mammography, ultrasound and MRI, if available)	✓	✓		
Breast Lesion Sizing: comparison against conventional imaging data (mammography, ultrasound)			✓	✓
Discrimination between malignant and benign breast lesions using features extracted from the MBI images	✓	✓	✓	✓
Safety and Tolerability	✓	✓	✓	✓

#### Primary Endpoint Analysis:

The first primary endpoint of this study is to gather exploratory data to refine the Wavelia investigational medical imaging device.

All the evolutions of Wavelia, as derived and/or confirmed using the data collected during this first-in-human study, will be clearly described, with associated rationale in the CSR, as part of the primary endpoint analysis for this study.

The second primary endpoint is to gather preliminary data on the safety profile of the investigational medical imaging device. All adverse event data will be described in the CSR.

#### Exploratory Endpoint Analysis:

In compliance with MDCG 2020-1 Guidance on Clinical Evaluation [18] and the International Medical Device Regulators Forum (IMDRF) [19], the Wavelia Breast Imaging technology is at the Stage 1 of the Clinical Evaluation of its MBI Quantitative Imaging function.

The exploratory endpoint of this proof-of-concept study is to collect meaningful data to support the Scientific Validity and verify the Clinical Association between the outputs of the Wavelia MBI Quantitative Imaging function and the patient's clinical condition, in terms of:

- Palpable Breast Lesion Detectability
- Palpable Breast Lesion Sizing,
- Potential for discrimination between malignant and benign breast lesions.

No quantitative performance results are intended as measurable outputs of the First-in-Human (FiH) study.

The assessment of the technical/analytical and clinical performance, correspond to the Stages 2 and 3 of the Clinical Evaluation of the Wavelia technology, which will be set as endpoints of subsequent clinical investigations.

## 7.5 DEFINITION OF END-OF-TRIAL

The end of trial will be the date of the data-base lock for the study, unless differently decided by the DSMB during the interim study assessment.

The end of the study will be reported to the REC and HPRA within 90 days, or 15 days if the study is terminated prematurely.

A summary report of the study will be provided to the REC and HPRA within 1 year of the end of the study.

## 8. SAFETY REPORTING

#### Evaluations of AEs and SAEs

Adverse Event Review will only occur once the patient is consented and deemed eligible for the study and continues until 7-21 days post investigational procedure or the participant is called to theatre for surgery, whichever happens first. All safety reporting must be carried out in compliance with the European Commission guidance document MEDDEV 2.7/3 and the harmonised standard EN ISO14155.

The investigator or delegate will record every Adverse Event (AE), Adverse Device Effect (ADE), Serious Adverse Event (SAE), Serious Adverse Device Effect (SADE) or observed device deficiency and report it to the sponsor together with an assessment. All AEs, ADEs, SAEs and SADEs will be reported to the Sponsor as per the timelines below, except for those identified below as not requiring immediate reporting.

For both AEs and SAEs each individual unintended sign, symptom or disease is considered a separate AE unless an overarching diagnosis can be made for a collection of signs or symptoms that are clinically linked and temporally related. The overarching diagnosis should be as specific as possible, using all available clinical data.

The investigator should use their clinical judgment to determine if an AE is of sufficient severity to require the subject's removal from the study. A subject may also voluntarily withdraw from study due to what she perceives as an intolerable AE. If either of these occurs, the subject must undergo an end-of-study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

## Definitions

The following definitions are outlined in the European Commission guidance document MEDDEV 2.7/3 and the harmonised standard EN ISO14155.

### Adverse Event

- An Adverse event (AE) is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device. This definition includes events related to the investigational device or the procedures involved in the present clinical protocol. The reporting of adverse events in users or other persons is restricted to events related to investigational medical devices.

### Adverse Device Effect

- An Adverse Device Effect (ADE) is defined as the adverse events related to the use of the investigational medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. It also includes any event that is a result of the use or error or intentional abnormal use of the investigational medical device.

### Serious Adverse Event

- Serious Adverse Events (SAEs) are defined as the adverse events that:
  - led to a death, injury or permanent impairment to a body structure or a body function.
  - led to a serious deterioration in health of the subject, that either resulted in:
    - a life-threatening\* illness or injury, or
    - a permanent impairment of a body structure or a body function, or
    - in-patient hospitalization or prolongation of existing hospitalization, or
    - in medical or surgical intervention to prevent life threatening illness

Life-threatening\* This refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Medically important\*\* Some medical events may jeopardise the subject or may require an intervention to prevent one of the above characteristics/consequences. Such events (hereinafter referred to as 'important medical events') should also be considered as 'serious' in accordance with the definition.

### Serious Adverse Device Effect

- Serious Adverse Device Effects (SADEs) are defined as the adverse device effects that have resulted in any of the consequences characteristic of a serious adverse event.

### Unanticipated Serious Adverse Device Effect

- An Unanticipated Serious Adverse Device Effects (USADE) is defined as a serious adverse device effect by their nature, incidence, severity or outcome that have not been identified in the current version of the risk analysis file.

### Device Deficiency

- A device deficiency includes any inadequacy of the investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

### Reportable Device Deficiency

A Device Deficiency is considered a reportable event if it might have led to a SAE had:

- Suitable action had not been taken
- Intervention had not been made
- If circumstances had been less fortunate

### Site Awareness

Serious adverse event, serious adverse device effects and reportable device deficiency information will be reported by site personnel to the sponsor within 3 calendar days from the time the site team becomes aware of the event, except for those that the protocol identifies as not requiring immediate reporting. The site team are considered aware of an adverse event from the time of first notification of the first member of the site team, as per the Site Delegation Log.

### Event Reporting

All events are reported to the sponsor by the completion of the relevant CRF in the eCRF. All AEs, ADEs, SAEs, and SADE, are reported on the AE CRF in the eCRF. All device deficiencies are reported on the device deficiency CRF in the eCRF. Supporting documentation may be requested by for any event reported.

In the event the eCRF is unavailable SAEs, SADEs and reportable device deficiencies should be completed on a paper copy of the CRF and submitted by email immediately but no later than 3 calendar days from site awareness of the event. The event should be completed in the database as soon as it becomes available.

### Assessment of Seriousness

The investigator or appropriately qualified member of the site team should assess the seriousness of an event as per the definition.

### Assessment of Severity

The investigator will make an assessment of severity for each AE, ADE, SAE and SADE and record this on the CRF according to one of the following categories:

- (1) **Mild:** An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with every day activities.
- (2) **Moderate:** An event that is sufficiently discomforting to interfere with normal everyday activities.
- (3) **Severe or medically significant:** An event that prevents normal everyday activities.
- (4) **Life threatening:** An event that has life-threatening consequences

Note: the term 'severe', should not be confused with 'serious' which is a regulatory definition based on subject/event outcome or action criteria.

### Timelines for Event Reporting

AEs, ADEs and device deficiencies (not meeting the criteria of a reportable device deficiency): Events will be reported by site personnel in a timely manner from the time the site becomes aware of the event.

SAEs, SADEs and Device Deficiencies (meeting the criteria of a reportable device deficiency): All SAEs, SADEs, and reportable Device Deficiencies should be reported to the sponsor immediately but no later than 3 calendar days from site awareness of the event.

### Follow Up

AEs and ADEs should be followed up until resolved, considered stable, or completion of subject participation in the study.

SAEs and SADEs will be followed up until resolution or they are clearly determined to be due to a participant's stable or chronic condition or intercurrent illness(es).

Device deficiencies and reportable device deficiencies will be followed up until resolution.

### Assessment of causality

All AEs judged by either the investigator or the sponsor as having a reasonable suspected causal relationship to the investigational medicinal device or procedures.

For the purpose of harmonising reports, all SAEs will be classified according to five different levels of causality. The sponsor and the investigators will use the following definitions to assess the relationship of the SAE to the investigational medical device or procedures. This assessment is carried out according to the following definitions:

- (1) **Not related:** relationship to the device or procedures can be excluded when:
  - The event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
  - The event has no temporal relationship with the use of the investigational device or the procedures;
  - The serious event does not follow a known response pattern to the medical device (if the response is previously known) and is biologically implausible;
  - The discontinuation of medical device application and reintroduction of its use do not impact on the serious event;
  - The event involves a body-site, or an organ not expected to be affected by the device or procedure;
  - The serious event can be attributed to another cause (e.g. an underlying or concurrent illness/clinical condition, an effect of another device, drug treatment or other risk factors);
  - The event does not depend on a false result given by the investigational device used for diagnosis when applicable;
  - Harms to the subject are not clearly due to use error;
  - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
- (2) **Unlikely:** the relationship with the use of this device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
- (3) **Possible:** the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying concurrent illness/clinical condition or/and an effect of another device, drug or treatment). Causes where

relatedness cannot be assessed, or no information has been obtained should also be classified as possible.

- (4) **Probable:** the relationship with the use of the investigational device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.
- (5) **Causal relationship:** the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:
- The event is a known side effect of the product category the device belongs to or of similar devices and procedures;
  - The event has a temporal relationship with investigational device use/application or procedures;
  - The event involves a body-site or organ that
    - The investigational device or procedures are applied to;
    - The investigational device or procedures have an effect on;
  - The serious event follows a known response pattern to the medical device (if the response pattern is previously known);
  - The discontinuation of medical device application and reintroduction of its use has an impact on the serious event;
  - Other possible causes (e.g. an underlying concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
  - Harm to the subject is due to error in use;
  - The event depends on a false result given by the investigational device used for diagnosis, when applicable;
  - In order to establish the relatedness, not all criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Any AEs/SAEs judged as having a reasonable suspected causal relationship (e.g. possible, probable or causal relationship) to the investigational medical device or procedures will be classified as an ADE/SADE.

#### Exemptions from Safety Reporting

There are no exemptions to safety reporting for participants in this study.

For participants in group 1 hospitalisation for surgery to the affected breast is a planned procedure at the time of enrolment into the study and therefore does not meet the criteria of a SAE. If any additional seriousness criteria are met this hospitalisation is reportable as a SAE.

#### Reporting by the investigator to the Sponsor

All AEs, ADEs and device deficiencies (that do not meet the definition of reportable device deficiencies) should be reported to the sponsor in a timely manner.

In compliance with the European Commission guidance document MEDDEV 2.7/3 Revision 3 and the harmonised standard EN ISO14155 all SAEs, SADEs and device deficiencies that meet the criteria of a reportable event will be fully recorded and reported to the Sponsor by the investigator immediately but no later than 3 calendar days after investigational site study personnel's awareness of the event.

The event report will be provided to the sponsor immediately, but no later than 3 calendar days after investigational site study personnel's awareness of the event.

## Reporting to the HPRA

The sponsor will be responsible for the classification of the adverse events, after reviewing the principal investigator's assessment under Annex X of Directive 93/42/EEC.

The Sponsor is responsible for the submission of reportable events to the HPRA and Ethics Committee. The reporting form template for the summary SAE tabulation, as given in the Appendix of the EC guidance document MEDDEV 2.7/3, will be updated and transmitted to the REC and HPRA each time a new reportable event or a new finding to an already reported event is to be reported.

The sponsor must adhere to the following timelines in the submission of reportable events to the HPRA and the Ethics Committee.

For all reportable events which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it should be reported to the HPRA immediately but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event.

All other reportable events should be reported to the HPRA immediately, but no later than 7 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event.

The sponsor will submit on request a safety report to the HPRA.

## Assessment of Expectedness

A list of all foreseeable adverse events and anticipated adverse device effects, together with their likely incidence, mitigation or treatment, have been included in the Risk Management File, after the completion of the Risk Analysis of the investigational medical imaging device.

An expectedness assessment will be carried out by the sponsor for each SADE according to the current versions of the risk management file.

## **9. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS**

Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

## **10. DATA HANDLING AND RECORD KEEPING**

Data will be shared only amongst the investigators involved in data collection, interpretation and analysis.

### **10.1 DATA COLLECTION, SOURCE DOCUMENTS AND CASE REPORT FORMS (CRF)**

Source documents for this study will include hospital records and procedure reports and data collection forms. These documents will be used to enter data on the case report form (CRF).

Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

All documents will be stored safely in a confidential and secure environment. On all study-specific documents other than the signed consent, the subject will be referred to by the study subject identification number/code.

## **10.2 DATA REPORTING**

The subjects will be identified by a study specific subjects number and/or code in the database. The name and any other identifying detail will not be included in any study data electronic file.

## **11. RETENTION OF ESSENTIAL DOCUMENTS**

Essential documents will be retained for 5 years or until at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. The documents will be retained for a longer period if required.

## **12. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES**

Quality assurance procedures will ensure management practices are in place to ensure that:

1. Every imaging procedure performed is necessary and appropriate, taking the patient into consideration.
2. The images and data generated contain information critical to further development.
3. The recorded information is correctly interpreted and made available in a timely fashion to those responsible for data interpretation.
4. The examination results in the lowest possible risk, cost, and inconvenience to the patient consistent with objectives above.

A quality control programme (QC program) will form an integral part of quality assurance. Quality control entails a distinct set of technical procedures that ensure the production of a satisfactory product, in this case, high-quality data for interpretation.

This will involve:

1. Initial testing to detect defects in the equipment once newly installed (to be verified and assured by the sponsor team).
2. Establishment of baseline performance of the equipment
3. Detection and diagnosis of changes in equipment performance prior to use
4. Identification of any issues with equipment performance on an ongoing basis and verification that the causes of deterioration in equipment performance have been corrected prior to re-use (call sponsor maintenance team if required).
5. A quality check using Data Quality Check software tool for both the OBCD and MBI subsystem will be undertaken, after completion of either scan. In case of non-optimal initial positioning of the patient and/or non-optimal patient position maintenance during the scan, the scan will be repeated.

A functional testing procedure will be carried out on the investigational medical imaging device after installation in the clinical site and/or after every maintenance operation.

## **13. INVESTIGATION MONITORING**

### **13.1 DIRECT ACCESS TO DATA**

The agreement with the Principal Investigator will include permission for investigation related monitoring, audits, ethics committee review and regulatory inspections, by providing direct access to source data and investigation related documentation. Consent from patients/legal representatives for

direct access to data will also be obtained. The patients' confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

## **13.2 MONITORING ARRANGEMENTS**

The CRFG will be responsible for investigation monitoring. On-site monitoring visits will be conducted in accordance with the clinical investigation monitoring plan. On-site monitoring will be an ongoing activity from the time of initiation until clinical investigation close-out and will comply with the principles of GCP and EU directive 93/42/EEC. The frequency and type of monitoring will be detailed in the monitoring plan and agreed by the trial Sponsor.

Before the clinical investigation starts, an initiation visit will take place to ensure that all relevant essential documents and supplies are in place and that site staff are fully aware of the clinical investigation protocol and SOPs. On site monitoring visits during the clinical investigation will check the completeness of patient records, the accuracy of entries on CRFs, the adherence to the protocol, SOPs and GCP, and the progress of patient recruitment. Monitoring will also ensure that the investigational device is being stored, and maintained according to specifications.

The Principal Investigator should ensure that access to all investigation related documents including source documents (to confirm their consistency with CRF entries) are available during monitoring visits. The extent of source data verification (SDV) will be documented in the monitoring plan."

## **14. AUDITS AND INSPECTIONS**

This trial may be subject to internal or external auditing or inspections procedure to ensure adherence to GCP. Access to all trial-related documents will be given at that time.

## **15. ETHICS**

### **15.1 DECLARATION OF HELSINKI**

The sponsor will ensure that this study is conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

### **15.2 GOOD CLINICAL PRACTICE**

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union (EU) Directive 93/42/EEC and EN ISO 14155.

### **15.3 APPROVALS**

Required documents including the protocol, informed consent form (ICF), patient information leaflet (PIL) and any other required documents will be submitted to a recognised research ethics committee and the competent regulatory authority (HPRA) for written approval.

The sponsor will submit and obtain approval from the above parties for substantial amendments to the original approved documents.

## **15.4 INFORMED CONSENT**

The investigator will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed, signed and dated by the subject, and by the person who administered the informed consent form.

## **15.5 BENEFITS AND RISKS ASSESSMENT**

The risks have been classified as physical, psychological, social, and economic.

- Physical Harms
  - Patients may be exposed to minimal exertion which may result in minor pain or discomfort when positioning themselves prone on the examining table
- Psychological Harms
  - Participation in research may prolong the normal emotional distress associated with frequenting a breast symptomatic unit. This may involve stress and feelings of embarrassment.
- Social and Economic Harms
  - This study should not result in any social or economic harm

Risk will be minimised by:

- Providing a comprehensive consent form explaining the experimental design and scientific rationale underlying the study.
- Involving a research team with expertise and experience.
- Incorporate adequate safeguards into the research design such as an appropriate data safety plan, the presence of trained personnel, and procedures to protect the confidentiality of the data (e.g., encryption, codes, and passwords).

## **15.6 SUBJECT CONFIDENTIALITY**

Subject data will be anonymized. All personal or identifiable details of the patient will be removed and the subject will be assigned a subject number. The data will be stored in encrypted software only accessible to those directly involved in the study. Subjects will be identified by a study specific subject number and/or code in the database. The name and any other identifying detail will not be included in any study data electronic file.

## **15.7 OTHER ETHICAL CONSIDERATIONS**

No additional ethical considerations.

## **16. FINANCING AND INSURANCE/INDEMNITY**

MVG holds Public Liability ('negligent harm') and Clinical Trial ('non-negligent harm') insurance policies which apply to this trial. MVG is funding this trial.

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